

What is claimed is:

*SAC 2*

1. An antibody-based fusion protein with an enhanced circulating half-life, comprising at least a portion of an immunoglobulin (Ig) heavy chain having substantially reduced binding affinity for an Fc receptor, said portion of heavy chain being linked to a second non-Ig protein, said antibody-based fusion protein having a longer circulating half-life *in vivo* than an unlinked second non-Ig protein.

2. The antibody-based fusion protein of claim 1, wherein said portion of heavy chain comprises at least the CH2 domain of an IgG2 or IgG4 constant region.

3. The antibody-based fusion protein of claim 1, wherein said portion of heavy chain comprises at least a portion of an IgG1 constant region having a mutation or a deletion at one or more amino acid selected from the group consisting of Leu<sub>234</sub>, Leu<sub>235</sub>, Gly<sub>236</sub>, Gly<sub>237</sub>, Asn<sub>297</sub>, and Pro<sub>331</sub>.

4. The antibody-based fusion protein of claim 1, wherein said portion of heavy chain comprises at least a portion of an IgG3 constant region having a mutation or a deletion at one or more amino acid selected from the group consisting of Leu<sub>281</sub>, Leu<sub>282</sub>, Gly<sub>283</sub>, Gly<sub>284</sub>, Asn<sub>344</sub>, and Pro<sub>378</sub>.

5. ~~The antibody-based fusion protein of claim 1, wherein said portion of heavy chain further has binding affinity for an immunoglobulin protection receptor.~~

6. The antibody-based fusion protein of claim 1, wherein said portion of heavy chain has substantially reduced binding affinity for a Fc receptor selected from the group consisting of Fc $\gamma$ RI, Fc $\gamma$ RII and Fc $\gamma$ RIII.

7. The antibody-based fusion protein of claim 1, wherein said second non-Ig protein is selected from the group consisting of a cytokine, a ligand-binding protein, and a protein toxin.

8. The antibody-based fusion protein of claim 1, wherein said cytokine is selected from the group consisting of a tumor necrosis factor, an interleukin, and a lymphokine.

9. The antibody-based fusion protein of claim 8, wherein said tumor necrosis factor is tumor necrosis factor alpha. ✓

10. The antibody-based fusion protein of claim 8, wherein said interleukin is interleukin-2. ✓

11. The antibody-based fusion protein of claim 8, wherein said lymphokine is a lymphotoxin or a colony stimulating factor.

12. The antibody-based fusion protein of claim 11, wherein said colony stimulating factor is a granulocyte-macrophage colony stimulating factor.

13. The antibody-based fusion protein of claim 1, wherein said ligand-binding protein is selected from the group consisting of CD4, CTLA-4, TNF receptor, and an interleukin receptor.

14. A method of increasing the circulating half-life of an antibody-based fusion protein, comprising the step of linking at least a portion of an Ig heavy chain to a second non-Ig protein, said portion of heavy chain having substantially reduced binding affinity for an Fc receptor, thereby forming an antibody-based fusion protein having a longer circulating half-life *in vivo* than an unlinked second non-Ig protein. ✓

15. The method of claim 14, wherein said portion of heavy chain comprises at least the CH2 domain of an IgG2 or IgG4 constant region.

16. A method of increasing the circulating half-life of an antibody-based fusion protein, comprising the steps of:

- introducing a mutation or a deletion at one or more amino acid of an IgG1 constant region, said amino acid selected from the group consisting of Leu<sub>234</sub>, Leu<sub>235</sub>, Gly<sub>236</sub>, Gly<sub>237</sub>, Asn<sub>297</sub>, and Pro<sub>331</sub>, thereby producing an Ig

heavy chain having substantially reduced binding affinity for an Fc receptor; and

(b) linking at least a portion of the heavy chain of step (a) to a second non-Ig protein,

thereby forming an antibody-based fusion protein having a longer circulating half-life *in vivo* than an unlinked second non-Ig protein.

17. A method of increasing the circulating half-life of an antibody-based fusion protein, comprising the steps of:

(a) introducing a mutation or a deletion at one or more amino acid of an IgG3 constant region, said amino acid selected from the group consisting of ~~Leu<sub>281</sub>, Leu<sub>282</sub>, Gly<sub>283</sub>, Gly<sub>284</sub>, Asn<sub>344</sub>, and Pro<sub>378</sub>~~, thereby producing an Ig heavy chain having substantially reduced binding affinity for an Fc receptor; and

(b) linking at least a portion of the Ig heavy chain of step (a) to a second non-Ig protein,

thereby forming an antibody-based fusion protein having a longer circulating half-life *in vivo* than an unlinked second non-Ig protein.

18. The method of claim 14, 16 or 17, wherein said portion of heavy chain further has binding affinity for an immunoglobulin protection receptor.

19. The method of claim 14, 16 or 17, wherein said portion of heavy chain has substantially reduced binding affinity for a Fc receptor selected from the group consisting of Fc $\gamma$ RI, Fc $\gamma$ RII and Fc $\gamma$ RIII.

20. The method of claim 14, 16 or 17, wherein said second non-Ig protein is selected from the group consisting of a cytokine, a ligand-binding protein, and a protein toxin.

21. The method of claim 14, 16 or 17, wherein said cytokine is selected from the group consisting of a tumor necrosis factor, an interleukin, and a lymphokine.

22. The method of claim 21, wherein said tumor necrosis factor is tumor necrosis factor alpha.

23. The method of claim 21, wherein said interleukin is interleukin-2.

24. The method of claim 21, wherein said lymphokine is a lymphotoxin or a colony stimulating factor.

25. ~~The antibody-based fusion protein of claim 24, wherein said colony stimulating factor is a granulocyte-macrophage colony stimulating factor.~~

26. The method of claim 14, 16 or 17, wherein said ligand-binding protein is selected from the group consisting of CD4, CTLA-4, TNF receptor, and an interleukin receptor.

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